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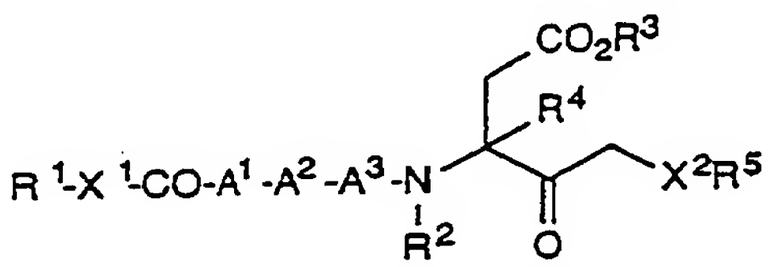
(54) Peptide inhibitors of pro-interleukin-1beta converting enzyme

(57) Compounds of the formula I:



I

or a pharmaceutically acceptable salt thereof, wherein R^1, R^2, R^3, R^4, R^5, A^1, A^1, A^2, A^3, and X^2, are as defined in the specification, together with pharmaceutical compositions for treatment of interleukin-1 mediated disorders or diseases comprising the compounds, are disclosed.

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Background to the Invention

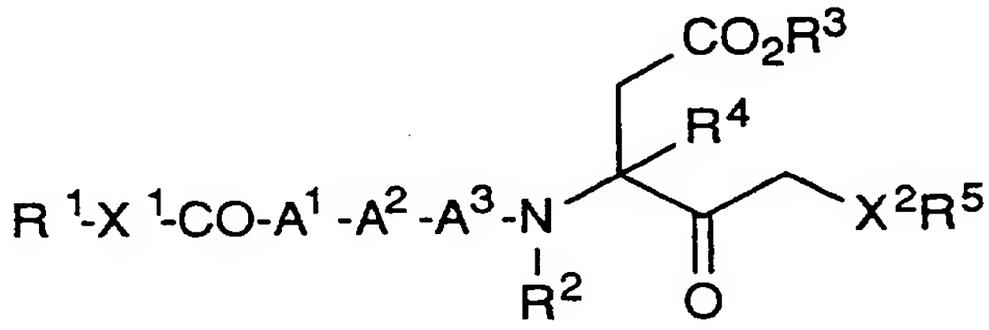
This invention relates to peptidic derivatives which are useful in the treatment of diseases in which IL-1 plays a central role. Interleukin-1 (IL-1) is a pro-inflammatory protein produced mainly by stimulated monocytes, although many other cell types have been shown to produce measurable quantities (Devine & Duff, *Immunology Today*, **1990**, 11, 13). IL-1 exists in two structurally distinct forms, IL-1α and IL-1β, each of mass 17,500 daltons but which show only 26% homology (March et al. *Nature*, **1985**, 315, 641). Each protein is synthesised in 31 kDa pro-form, and these are subsequently processed to their respective mature forms. Most IL-1α remains cell associated whereas 60 - 70% of IL-1β is released within 6 h of synthesis (di Giovine et al. *Lymphokine Res.* **1988**, 7, 271, and Hazuda et al. *J. Biol. Chem.* **1988**, 263, 8473). Both polypeptides interact with the same receptors giving rise to responses which are species- and tissue-dependant (Dinarello, *Blood*, **1991**, 77, 1627). However, whereas both pro-IL-α and its mature form are fully active, pro-IL-1β is completely inactive and processing to the mature form is required before the protein will bind to its receptor (Mosley et al. *J. Biol. Chem.* **1987**, 262, 2941). It is now known that a cytoplasmic enzyme, termed pro-IL-1β converting enzyme (ICE) is responsible for generating IL-1β in its mature form. This enzyme has been isolated from THP-1 human monocytic cells (Cenetti et al. *Science*, **1992**, 256, 97; Miller et al. *J. Biol. Chem.* **1993**, 268, 18062) and its gene has been cloned (Thornberry et al. *Nature*, **1992**, 356, 768).

It has been shown that ICE is a cysteine protease which shows little homology to any known protein, including cellular cysteine and serine proteases (Thornberry et al. **1992**). ICE cleaves pro-IL-1β at two sites, Asp^{27} - Gly^{28} and Asp^{116} - Ala^{117}, thus exhibiting a unique specificity. Other enzymes present in synovial fluid of patients with inflammatory disorders have been shown to cleave pro-IL-1β to give active forms with an additional 3 or 13 amino acids (Hazuda et al. *J. Biol. Chem.* **1990**, 265, 6318), but these events can only occur after secretion of pro-IL-1β from cells.

It is evident then, that compounds which are capable of inhibiting ICE activity would have the ability to prevent processing of pro-IL-1β to its active pro-inflammatory form, and thus would be useful in the treatment of diseases which are mediated or exacerbated by IL-1. Examples of such disease states include but are not limited to rheumatoid arthritis, encephalitis, inflammatory bowel disease, pancreatitis, psoriasis, hypotensive shock, Alzheimer's disease, sepsis, diabetes, immune complex glomerulonephritis, hepatitis, Crohn's disease, periodonitis, conditions involving T-cells, auto-immune diseases and reperfusion injury.

Description of the Invention

Novel peptidyl derivatives of formula I are potent inhibitors of ICE and are useful for treating diseases in which IL-1 plays a central role. The compounds differ for example from those of EP 0 519 748 A2, EP 0 529 713 A1, EP 0 547 699 A1, WO 93/16710, WO 93/09135 and WO 93/14777 in that they contain novel functionality at their C-terminus which act as powerful recognition and binding sites for the enzyme, making them significantly more potent inhibitors than those previously described. The present invention provides compounds of formula I:



I

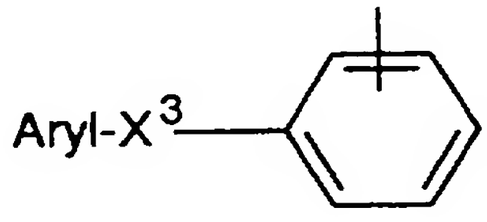
or a pharmaceutically acceptable salt thereof wherein:

R^1 is

(a) substituted (saturated or unsaturated) alkyl C_1 - C_{12}, wherein the substituents are selected from hydrogen, halogen, hydroxy, C_1 - C_6 alkoxy, C_1 - C_6 alkylcarbonyl and phenyl;

(b) aryl or aryl C_1 - C_6 (saturated or unsaturated) alkyl wherein the aryl group is selected from phenyl, napthyl, pyridyl, furyl, thienyl, thiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, benzofuryl, benzothienyl, pyrazolyl, indolyl, purinyl, isoxazolyl, oxazolyl, quinoxalinyl, triazolyl and triazinyl, and mono and di-substituted aryl as defined above wherein the substituents are independently C_1 - C_6 alkyl, halo, hydroxy, NR^6R^7, C_1 - $_6$ alkoxy, C_{1-6} alkylthio, C_1 - $_6$ alkylcarbonyl, carboxy or phenyl;

(c)



II;

wherein aryl is defined as in (b) above, and may be substituted as defined in (b) above.

R^2 is hydrogen, alkyl C_{1-4}, benzyl;

R^3 is hydrogen, alkyl C_{1-4} or phenyl;

R^4 is hydrogen, fluorine, C_{1-4} alkyl, $-(CH_2)_a-CO_2H$;

R^5 is

(a) substituted (saturated or unsaturated) alkyl C_{1-10}, wherein the substituents are selected from hydrogen, halogen, hydroxy, C_{1-6} alkoxy;

(b) aryl alkyl C_{1-6} (saturated or unsaturated) wherein the alkyl groups may be substituted by hydrogen, halogen or hydroxy and the aryl group is selected from phenyl, pyridyl, napthyl, furtyl, thienyl, pyrazinyl or pyrimidinyl, and is optionally mono or di-substituted with the substituents being selected independently from C_{1-6} alkyl, halo, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylcarbonyl, carboxy or phenyl;

(c) aryl or substituted aryl as defined in (b) above, subject to R^4 not being hydrogen and/or at least two of A^1, A^2 and A^3 being absent, and/or X^2 being -OCONH- or -NHCONH-;

R^6 and R^7 are independently hydrogen or C_{1-4} alkyl;

R^8, R^{10} and R^{12} are each independently selected from hydrogen or alkyl C_{1-6};

R^9, R^{11} and R^{13} are each independently selected from

(a) hydrogen

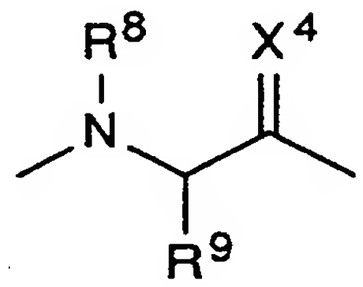
(b) substituted saturated or unsaturated alkyl C_{1-6}, wherein the substituent is selected from hydrogen, hydroxy, halo, -SH, $-S-C_{1-4}$ alkyl, C_{1-6} alkylcarbonyl, carboxy, $-CONH_2$, amino, C_{1-4} alkylamino, guanidino, $-O-C_{1-4}$ alkyl;

(c) aryl or aryl C_{1-6} alkyl, wherein aryl is defined as above for R^1 and wherein the aryl is optionally mono and di-substituted, the substituents being each independently C_{1-4} alkyl, halo, hydroxy, CO_2H, Me_2N-, NH_2, C_{1-4} alkylamino, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkyl carbonyl, NO_2, -SH or -CN;

A^1 is selected from

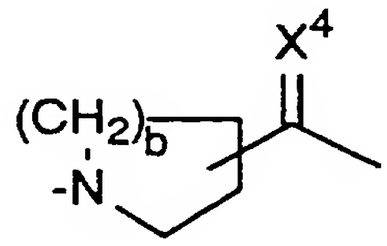
(a) a single bond;

(b) an amino acid residue or analogue of formula III;



III

(c) an imino acid residue or analogue of formula IV;

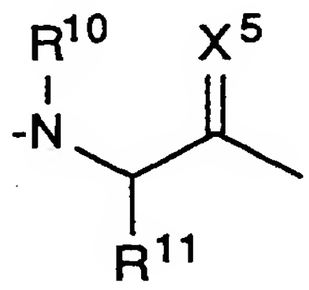


IV

A^2 is selected from

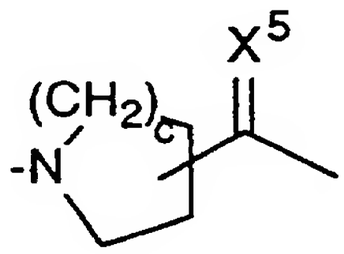
(a) a single bond;

(b) an amino acid residue or analogue of formula V;



V

(c) an imino acid residue or analogue of formula VI;

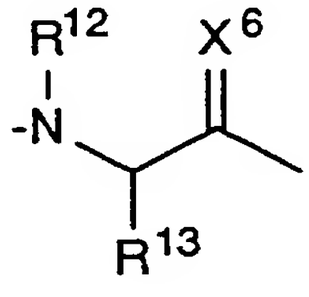


VI

A^3 is selected from

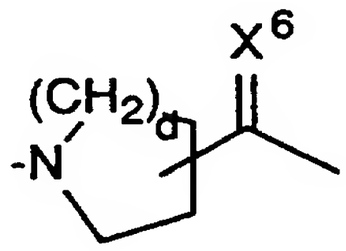
(a) a single bond;

(b) an amino acid residue or analogue of formula VII;



VII

(c) an imino acid residue or analogue of formula VIII



VIII

X^1 is absent, -O- or -NH-;

X^2 is -O-, -S-, -OCONH-, -$NHCO_2$- or -NHCONH-;

X^3 is absent, -NH-, -$(CH_2)_e$-, -$(CH_2)_e$O-, -O$(CH_2)_e$-, -CH=CH-, -CO$(CH_2)_e$-, -$(CH_2)_e$CO-, -$(CH_2)_e$NHCO-, -NHCO$(CH_2)_e$-, -$(CH_2)_e$CONH-, -CONH$(CH_2)_e$-, -$(CH_2)_e$$NHSO_2$-, -$NHSO_2(CH_2)_e$-, -$SO_2NH(CH_2)_e$-, -$(CH_2)_e$$SO_2NH$-, -$(CH_2)_e$NH-, -NH$(CH_2)_e$-;

X^4, X^5 and X^6 are each independently O or H_2;

a is 0 - 3
b is 0 - 4
c is 0 - 4
d is 0 - 4
e is 0 - 3
f is 0 - 2

Preferably

A^1 is a residue of tyrosine, phenylalanine, homophenylalanine, phenylglycine, tryptophan or histidine;

R^1 is unsubstituted C_{1-6} alkyl;

X^1 is absent, and other substituents are as described above;

Or more preferably

R^4 is hydrogen;

R^5 is substituted alkyl C_{1-10}, wherein the substituents are selected from hydrogen, halogen, hydroxy, C_{1-6} alkoxy or phenyl;

X^2 is O or S, and the other substituents are as described above.

Another preferred embodiment of the invention is when

R^1 is aryl or aryl C_{1-6} (saturated or unsaturated) alkyl wherein the aryl group is selected from phenyl, napthyl, pyridyl, furyl, thienyl, pyrazinyl, pyrimidinyl, pyrazolyl and indolyl, and mono and disubstituted aryl as defined above wherein the substituents are independently C_{1-6} alkyl, halo, hydroxy, NR^6R^7, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkyl carbonyl, carboxy or phenyl;

A^1 is absent;

Or more preferably

R^4 is hydrogen;

R^5 is substituted alkyl C_{1-10}, wherein the substituents are selected from hydrogen, halogen, hydroxy, C_{1-6} alkoxy, or phenyl;

X^2 is O or S.

Amongst preferred compounds according to the invention are those listed below and salts thereof:

(3S)-3-(Acetyl-tyrosinyl-valyl-alanyl)amino-4-oxo-5-(2',2',2'-trifluoroethoxy) pentanoic acid;

(3S)-3-(Acetyl-tyrosinyl-valyl-alanyl)amino-4-oxo-5-^{n}propyloxy pentanoic acid;

(3S)-3-(Acetyl-tyrosinyl-valyl-alanyl)amino-5-ethoxy-4-oxo pentanoic acid;

(3S)-3-(Benzyloxycarbonyl-valyl-alanyl)amino-4-oxo-5-(2',2',2'-trifluoroethoxy) pentanoic acid;

(3S)-3-(Benzyloxycarbonyl-valyl-alanyl)amino-5-methoxy-4-oxo pentanoic acid;

(3S)-3-(Benzyloxycarbonyl-valyl-alanyl)amino-5-^{n}butyloxy-4-oxo pentanoic acid;

(3S)-3-(Benzyloxycarbonyl-valyl-alanyl)amino-5-ethoxy-4-oxo pentanoic acid;

(3S)-3-(Benzyloxycarbonyl-phenylalanyl-alanyl)amino-4-oxo-5-(2',2',2'-trifluoroethoxy) pentanoic acid;

(3S)-3-(Benzyloxycarbonyl-homophenylalanyl-alanyl)amino-4-oxo-5-(2',2',2'-trifluoroethoxy) pentanoic acid;

(3S)-3-(Benzyloxycarbonyl-norleucinyl-alanyl)amino-4-oxo-5-(2',2',2'-trifluoroethoxy) pentanoic acid;

(3S)-3-(Benzyloxycarbonyl-prolyl-alanyl)amino-4-oxo-5-(2',2',2'-trifluoroethoxy) pentanoic acid;

(3S)-3-(Benzyloxycarbonyl-phenylglycinyl-alanyl)amino-4-oxo-5-(2',2',2'-trifluoroethoxy) pentanoic acid;

(3S)-3-(Benzyloxycarbonyl-leucinyl-alanyl)amino-4-oxo-5-(2',2',2'-trifluoroethoxy) pentanoic acid;

(3S)-3-(Benzyloxycarbonyl-isoleucinyl-alanyl)amino-4-oxo-5-(2',2',2'-trifluoroethoxy) pentanoic acid;

(3S)-3-(Benzyloxycarbonyl-cyclohexylglycinyl-alanyl)amino-4-oxo-5-(2',2',2'-trifluoroethoxy) pentanoic acid;

(3S)-3-(Benzyloxycarbonyl-valyl-isoleucyl)amino-4-oxo-5-(2',2',2'-trifluoroethoxy) pentanoic acid;

(3S)-3-(Benzyloxycarbonyl-valyl-norleucyl)amino-4-oxo-5-(2',2',2'-trifluoroethoxy) pentanoic acid;

(3S)-3-(Benzyloxycarbonyl-valyl-homophenylalanyl)amino-4-oxo-5-(2',2',2'-trifluoroethoxy) pentanoic acid;

(3S)-3-(Benzyloxycarbonyl-valyl-valyl)amino-4-oxo-5-(2',2',2'-trifluoroethoxy) pentanoic acid;

(3S)-3-(Benzyloxycarbonyl-valyl-propyl)amino-4-oxo-5-(2',2',2'-trifluoroethoxy) pentanoic acid;

(3S)-5-Methoxy-4-oxo-3-(3'-phenylpropanoyl-valyl-alanyl)amino pentanoic acid;

(3S)-5-Ethoxy-4-oxo-3-(3'-phenylpropanoyl-valyl-alanyl)amino pentanoic acid;

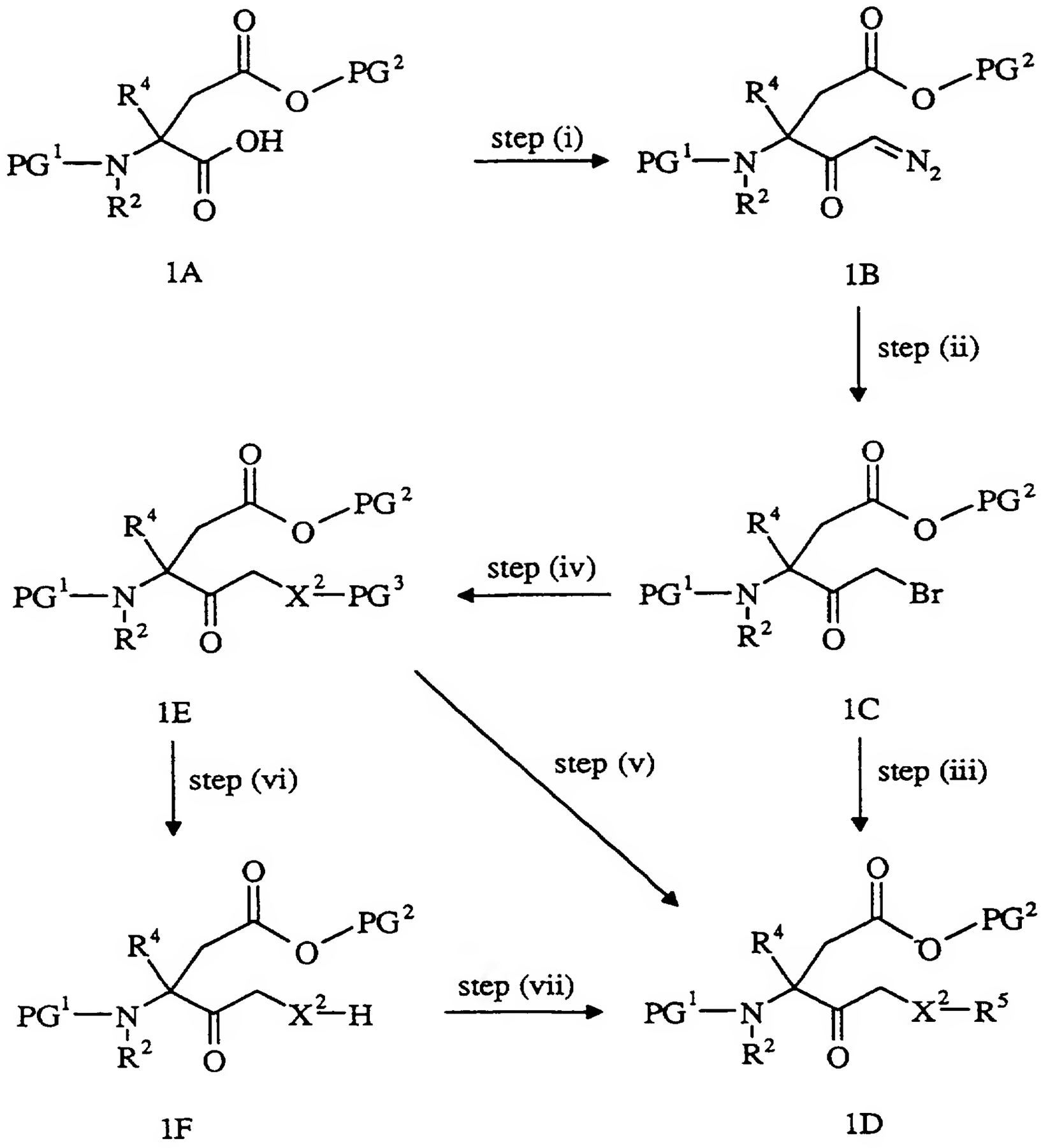
(3S)-3-(Benzoyl-valyl-alanyl)amino-5-^{n}butyloxy-4-oxo pentanoic acid;

(3S)-3-(Benzoyl-valyl-alanyl)amino-5-benzyloxy-4-oxo pentanoic acid;

(3S)-3-(Benzoyl-valyl-alanyl)amino-4-oxo-5-(3'-hydroxypropyloxy) pentanoic acid.

The compounds of the invention can be prepared using general methods outlined in the schemes below, and further illustrated with specific, non-limiting examples.

Scheme 1



1A 1B 1C 1D 1E 1F

in which R^2, R^4, R^5 and X^2 are as defined previously; PG^1 is an amine protecting group (for example benzyloxycarbonyl or t-butyloxycarbonyl); PG^2 is a carboxylic acid protecting group (for example an alkyl group which forms a readily hydrolysable ester), provided that PG^2 is stable under conditions used to remove PG^1; and PG^3 is a group chosen such that it facilitates the introduction of X^2 and it can either be removed under conditions that leave PG^1 and PG^2 intact or it can be directly transformed into R^5.

In step (i) an aspartic acid analogue 1A is converted into a diazomethyl ketone 1B. This is accomplished in two steps. The acid is first converted into a more active acylating species; for example an acyl chloride (by reaction with eg. oxalyl chloride or thionyl chloride) or a mixed anhydride (by reaction with eg. isobutyl chloroformate). This acylating species is then reacted with diazomethane to give 1B.

In step (ii) the diazoketone 1B is converted into the bromomethyl ketone 1C. This is conveniently accomplished by treating 1B with an anhydrous solution of hydrogen bromide in a convenient solvent (for example ethyl acetate or diethyl ether).

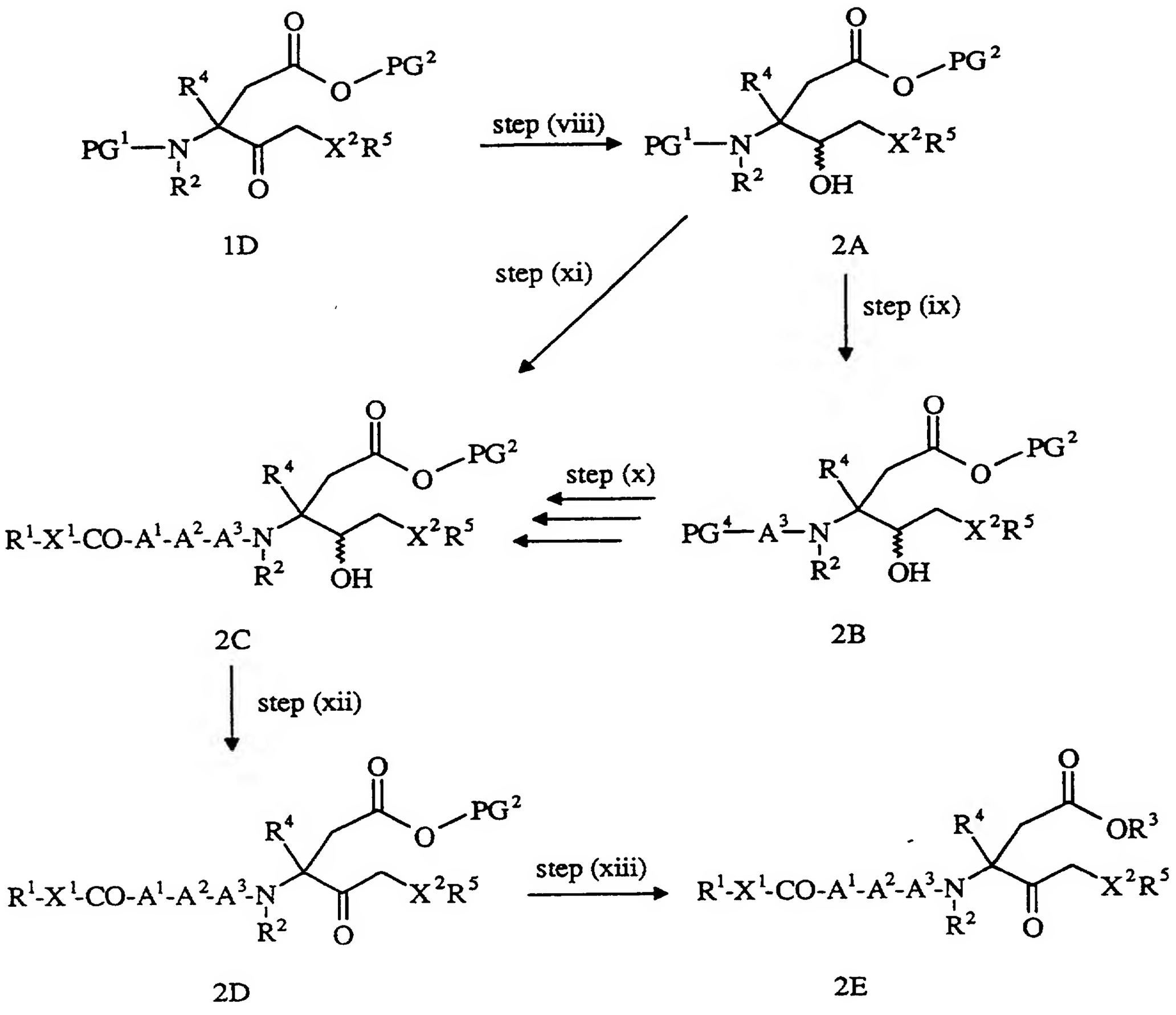
Elaboration of 1C into 1D depends on the precise nature of the group R^5X^2-. In some cases a single step is sufficient. In these cases the route followed is via step (iii). This involves the reaction of 1C with the chemical entity R^5X^2-H, usually in the presence of a base. One example of this is the case where $R^5 = CF_3CH_2$- and X^2 = -O-. The chemical entity R^5X^2-H is then 2,2,2-trifluoroethanol, which reacts with bromomethyl ketones in the presence of bases such as cesium fluoride and sodium hydride.

If direct reaction of 1C with R^5X^2-H is not a viable process then a less direct scheme is adopted. In step (iv) the bromomethyl ketone 1C is reacted with a species PG^3-X^2-H which introduces the group X^2 into 1E but which requires further manipulation to elaborate R^5. For example in many cases where X^2 = -O- the direct route of step (iii) is inappropriate due to the high basicity or low nucleophilicity of R^5-X^{2-}, the anion corresponding to R^5X^2-H. The use of a more nucleophilic, less basic, carboxylate anion is often better. Benzoylformate ($PhCOCO_2$-) is one prefered option. This would give 1E in which PG^3- is PhCOCO-. Another example is the case where X^2 is -NHCONH-. Displacement of the bromide from 1C with a nitrogen nucleophile requires the careful selection of reagents. It can be achieved by reagents such as, for example, sodium azide and potassium cyanate when the group -X^2PG^3 would be -N_3 and -NCO respectively.

Conversion of 1E to 1D will require either one or two further operations. Step (v) represents the one step procedure. This requires that $-X^2PG^3$ be able to be transformed directly into $-X^2R^5$. One example of this is the case discussed above in which $-X^2PG^3$ is -NCO. This compound is capable of reacting with an amine R^5NH_2 to give a urea 1D in which X^2 is -NHCONH-.

More frequently two operations are required. In step (vi) the group $-PG^3$ is removed. This can be achieved by the application of a number of different treatments. For example when X^2 is -O- and PG^3- is PhCOCO- the use of alkaline hydrolysis is a prefered method. This liberates an alcohol. When $-X^2PG^3$ is $-N_3$ a reductive method, for example hydrogenolysis over a catalyst, can be used to liberate an amine 1F in which $-X^2$-H is $-NH_2$. Step (vii) represents the final elaboration of 1D from 1F. Again the reagents and conditions chosen depend on the precise nature of R^5 and X^2. Continuing with the two examples above, when 1F is an alcohol (i.e. when $-X^2$-H is OH) it can be treated with an alkylating agent, for example an alkyl iodide or alkyl bromide, in the presence of a base to give an ether 1D in which X^2-R^5 is -O-alkyl. When 1F is an amine (i.e. when $-X^2$-H is NH_2) it will react with an isocyanate R^5NCO to give a urea 1D in which $-X^2$-R^5 is -NHCONH-R^5.

Scheme 2



1D 2A 2B 2C 2D 2E

in which A^1, A^2, A^3, R^1, R^2, R^3, R^4, R^5, X^1, X^2, PG^1 and PG^2 are as defined previously and PG^4 is an amine protecting group as defined for (but not necessarily identical with) PG^1. It is usually found that elaboration of 1D proceeds better if the ketone is temporarily masked by reduction to the secondary alcohol 2A. This is represented in step (viii). The reagent used is chosen from any of the reagents known to achieve this conversion. Complex metal hydrides are examples of such reagents. One prefered reagent is sodium borohydride.

The further elaboration of 2A can either be a stepwise process or a single operation. Most often the stepwise protocol is prefered. In step (ix) PG^1 is removed from the amino group of 2A. The amine is then coupled to a protected amino acid corresponding to A^3. Any incompatible functionality in A^3 is suitably protected prior to this coupling. The reagents chosen for the removal of PG^1 and the coupling of A^3 can be any of those known to achieve these conversions. Step (x) represents the iterative addition of further residues to the growing chain by the repetition of the transformations of step (ix). Step (xi) represents the single-step alternative to steps (ix) and (x). The preformed fragment corresponding to R^1-X^1-CO-A^1-A^2-A^3, with any incompatible functionality protected, is coupled directly onto the amine obtained by the deprotection of 2A. In the final steps in the sequence 2C is elaborated into 2E by oxidation to restore the ketone and by deprotection. Step (xii) is the oxidation of alcohol 2C to give the ketone 2D. The reagent used is selected from any of the usual oxidising agents which achieve this transformation. A prefered reagent is an iodine (III) species derived from ortho-iodobenzoic acid and commonly called the Dess-Martin periodinane. Step (xiii) involves the removal of all remaining protecting groups. These include PG^2 and any groups used to protect, for example, the residues A^1, A^2 and A^3. Preferably these will have been chosen such that their removal requires only one operation. For example, when A^1 is tyrosine the hydroxyl group has to be protected during the couplings. If it is protected as a tert-butyl ether then choosing PG^2 to be tert-butyl allows both protecting groups to be removed by a single acid treatment.

The preceding general methods are further illustrated in the following non-limiting Examples.

GENERAL METHODS

NMR: Proton nuclear magnetic resonance spectra were recorded at 270 MHz. Samples were dissolved in deuterochloroform unless otherwise stated. Chemical shifts are reported relative to Me_4Si (δ=0).

MS: Mass spectra were recorded in positive ion mode using fast atom bombardment ionization. The peak reported corresponds to $[M+H]^+$ unless otherwise stated.

HPLC: High pressure liquid chromatographic analysis of products was carried out on a Spherisorb C_{18} column; particle size 5μ; column dimensions 4.6 x 100 mm.

Eluant A: 0.1% TFA in water,

Eluant B: 0.1% TFA in acetonitrile

In the Tables:

Gradient A: 20% to 80% B into A in 25 mins at 0.8 mL/min

Gradient B: 40% to 90% B into A in 25 mins at 0.8 mL/min

Gradient C: 30% to 90% B into A in 25 mins at 0.8 mL/min

Gradient D: 10% to 70% B into A in 25 mins at 0.8 mL/min

MPLC: Medium pressure liquid chromatographic purification of products was carried out on a Vydac C_{18} column using the eluants A and B described above. In the Tables the figures give the initial and final proportion (%) of B in the eluant.

Column: In the Tables this refers to flash chromatography on silica gel. The following abbreviations are used:

A	acetic acid
C	chloroform
E	ethyl acetate
H	hexane fraction
M	methanol
P	petroleum ether

AAA: Aminoacid analysis: peptides were hydrolyzed for 90 min at 150°C in 6*N* HCl + phenol; PC is the peptide content.

Example 1: (3S)-3-(Benzyloxycarbonylvalylalanylamino)-6-oxa-4-oxo-8,8,8-trifluorooctanoic acid

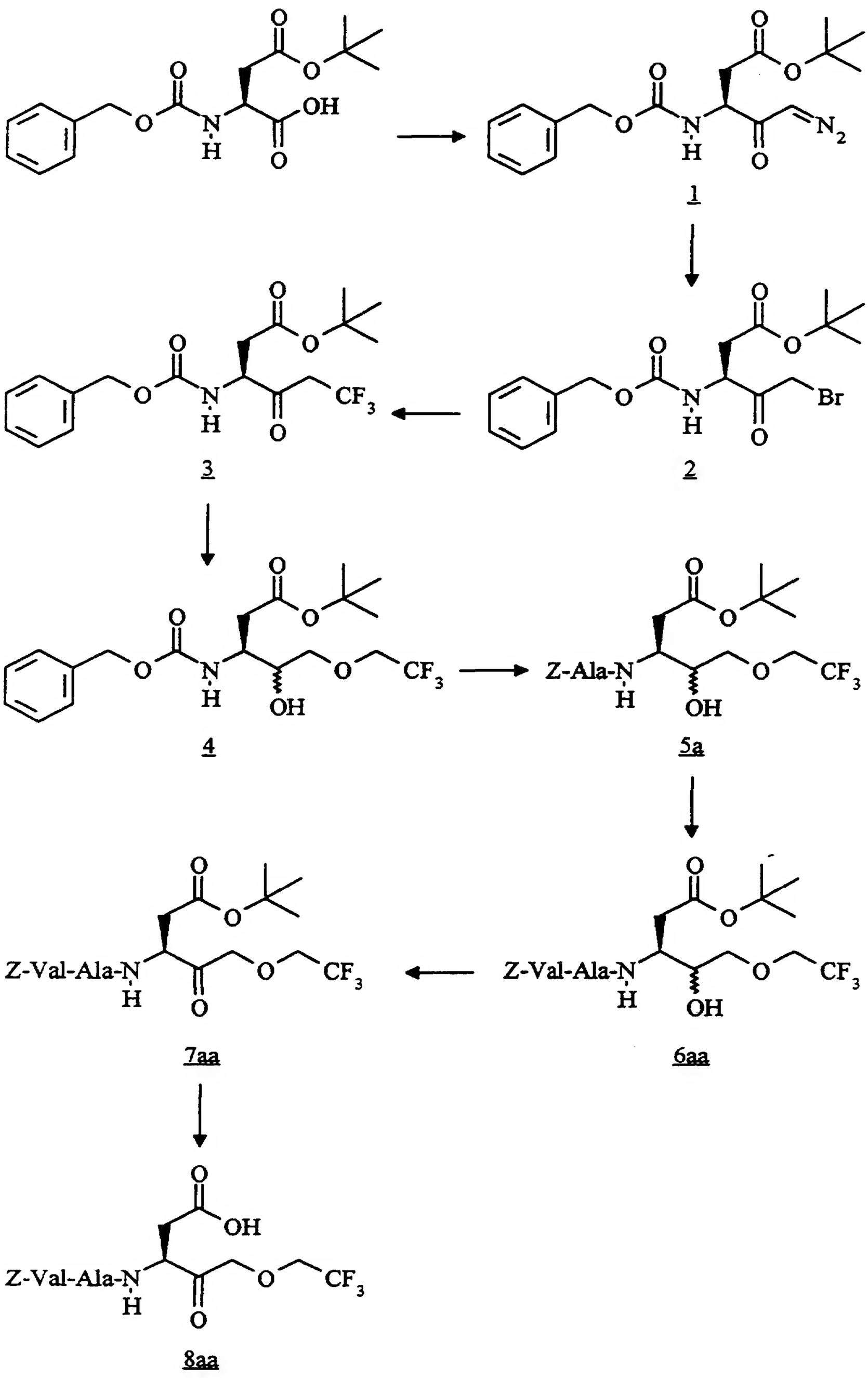
1A: *tert*-Butyl (3S)-3-(benzyloxycarbonylamino)-5-diazo-4-oxo-pentanoate (1)

To a cold (-20°C) stirred solution of Z-Asp(O-t-Bu)OH (29.1 g, 90 mmol) in ethyl acetate (100 mL) was added N-methylmorpholine (10.4 mL, 95 mmol) and isobutyl chloroformate (12.25 mL, 95 mmol). Stirring was continued for 40 min while the temperature of the reaction mixture was maintained between -20°C and -15°C. The mixture was filtered and the filtrate was added to an ice-cold ethereal solution of diazomethane (generated from 38.7 g, 180 mmol of Diazald®). The resulting solution was allowed to warm to room temperature and stirred for 2 hr before the excess diazomethane was destroyed by the dropwise addition of acetic acid. The mixture was washed with 5% aqueous $KHCO_3$, water and brine, filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel eluting with 25:75 EtOAc:hexane.

Because of its potential thermal instability no attempt was made to remove all traces of solvent from the diazoketone, hence no meaningful yield could be recorded.

1B: *tert*-Butyl (3S)-3-(benzyloxycarbonylamino)-5-bromo-4-oxo-pentanoate (2)

To an ice-cold stirred solution of diazoketone 1 in ethyl acetate (250 mL) was added dropwise a saturated solution of HBr in ethyl acetate until the yellow coloration had disappeared and evolution of N_2 had ceased. The solution was washed with 5% aqueous $KHCO_3$, water and brine, filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel eluting with 25:75 EtOAc:hexane, to give the title bromomethyl ketone as a colourless oil which crystallises on standing (28.0 g, 78% over 2 steps).



1

2

3

4

5a

6aa

7aa

8aa

1C: *tert*-Butyl (3S)-3-(benzyloxycarbonylamino)-6-oxa-4-oxo-8,8,8-trifluorooctanoate (3)

To a stirred solution of bromomethyl ketone 2 (6.0 g, 15 mmol) in DMF (25 mL) was added 2,2,2-trifluoroethanol (1.31 mL, 18 mmol) and cesium fluoride (3.42 g, 22.5 mmol). The mixture was stirred at room temperature for 18 hr then the solvent was evaporated in vacuo and the residue was partitioned between EtOAc and brine. The organic layer was filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel eluting with 20:80 EtOAc:hexane to give the title ketone as a colourless oil (3.2 g, 51%).

^{1}H NMR ($CDCl_3$) δ 4.55 and 4.40 (isolated AB), 4.10 (s), 3.85 (q), 2.95 and 2.85 (ABX_n).

The NMR spectrum of this compound is complex and indicates that a mixture of at least two components is present, presumably ketone and hydrate. Only selected peaks are reported.

1D: *tert*-Butyl (3S, 4RS)-3-(benzyloxycarbonylamino)-4-hydroxy-6-oxa-8,8,8-trifluorooctanoate (4)

To a cold (-20°C) stirred solution of the ketone 3 (3.20 g, 7.6 mmol) in methanol (25 mL) was added $NaBH_4$ (290 mg, 7.6 mmol). The mixture was allowed to warm to room temperature and stirred for 1 hr then quenched by the addition of 2 M aqueous NH_4Cl (75 mL). The mixture was extracted 3 times with EtOAc. The combined extracts were washed with brine, filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel eluting with 30:70 EtOAc:hexane to give the title compound as a white amorphous solid (1.95 g, 61%).

^{1}H NMR ($CDCl_3$) δ 4.15 - 4.00 (2H, m); 3.65 - 3.50 (2H, m).

1E: *tert*-Butyl (3S, 4RS)-3-(benzyloxycarbonylalanylamino)-4-hydroxy-6-oxa-8,8,8-trifluorooctanoate (5a)

This was prepared from the protected aminoalcohol 4 on a 1.47 mmol scale using standard solution phase peptide coupling techniques. 4 was deprotected by catalytic hydrogenolysis over 10% Pd-on-C in methanol. The resultant amine was isolated by filtration and evaporation of the solvent, then coupled to Z-Ala-OH using the hydroxybenzotriazole/water-soluble carbodiimide methodology. The product was purified by flash chromatography on silica gel eluting with 55:45 EtOAc:hexane and isolated in 66% yield.

1F: *tert*-Butyl (3S, 4RS)-3-(benzyloxycarbonylvalylalanylamino)-4-hydroxy-6-oxa-8,8,8-trifluorooctanoate (6aa)

This was prepared from 5a on a 0.96 mmol scale by deprotection and subsequent coupling to Z-Val-OH following the method outlined in Example 1E. The product was isolated in 48% yield after flash chromatography on silica gel eluting with 75:25 EtOAc:hexane.

1G: *tert*-Butyl (3S)-3-(benzyloxycarbonylvalylalanylamino)-6-oxa-4-oxo-8,8,8-trifluorooctanoate (7aa)

To a stirred solution of the alcohol 6aa (280 mg, 0.47 mmol) in dichloromethane (10 mL) was added 1,1,1-tris(acetoxy)-1-ioda-3-oxoisobenzofuran (Dess-Martin periodinane, 400 mg, 0.95 mmol). The mixture was stirred at room temperature for 3 days then diluted with EtOAc (20 mL). To this mixture was added a solution of sodium thiosulphate in saturated aqueous sodium hydrogencarbonate (15 mL). Stirring was continued for 20 min then the phases were separated and the aqueous layer was extracted twice with EtOAc. The organic layers were combined and washed once with the sodium thiosulphate/sodium hydrogencarbonate mixture, then with water and brine, filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel eluting with 65:35 EtOAc:hexane to give the title compound as an amorphous solid (215 mg, 77%).

1H: (3S)-3-(Benzyloxycarbonylvalylalanylamino)-6-oxa-4-oxo-8,8,8-trifluorooctanoic acid (8aa)

To a stirred solution of 7aa (215 mg, 0.36 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (20 mL). The mixture was stirred for 1 hr then concentrated in vacuo. The residue was purified by repeated MPLC on a Vydac C_{18} column eluting first with a gradient of 30:70:0.1 to 90:10:0.1 MeCN:H_2O:TFA and subsequently with a gradient of 20:80:0.1 to 80:20:0.1 MeCN:H_2O:TFA, to give the title compound as an amorphous solid (94 mg, 49%).

HPLC: Gradient 20 to 80% B into A in 25 min at 0.8 mL/min.
Peak detected at 17.9'.

A.A.A.: Found: Ala 0.96; Val 1.04.
P.C. = 87%.

M.S. $[M+H]^+ = 534.3$.

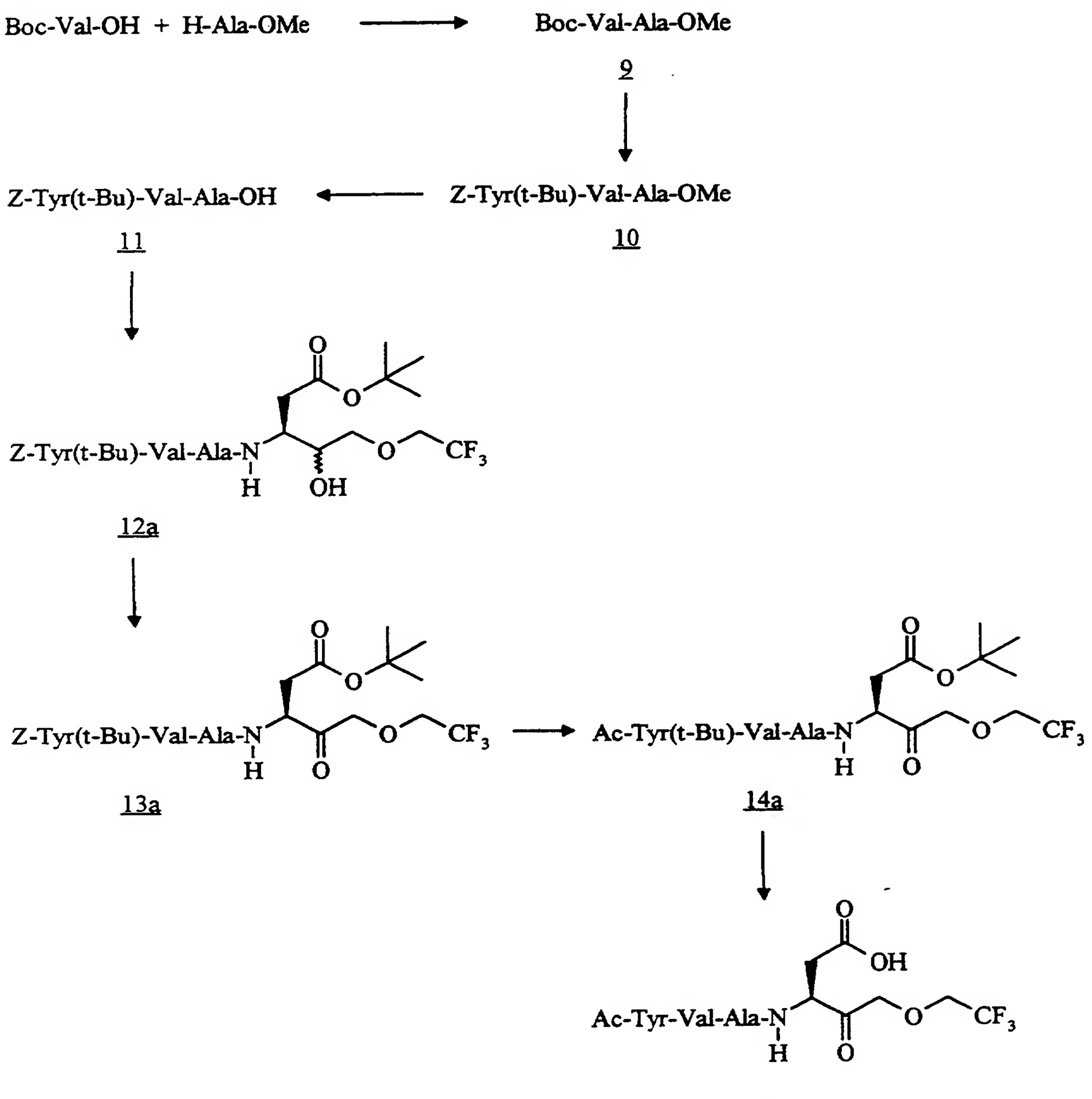
Example 2: (3S)-3-(Acetyltyrosinylvalylalanylamino)-6-oxa-4-oxo-8,8,8-trifluorooctanoic acid

2A: *tert*-Butyloxycarbonylvalylalanine methyl ester (9)

This was prepared from Boc-Val-OH and H-Ala-OMe on a 8.7 mmol scale using the standard hydroxybenzotriazole/water-soluble carbodiimide methodology. The product was used without purification, assuming a quantitative yield.

2B: Benzylcarbonyl (O-*tert*-butyltyrosinyl)valylalanine methyl ester (10)

This was prepared from 9 on a 8.7 mmol scale by deprotection with 4N HCl/dioxan followed by coupling to Z-Tyr(t-Bu)-OH using the standard hydroxybenzotriazole/water-soluble carbodiimide methodology. The product was isolated in 65% yield after flash chromatography on silica gel eluting with 65:35 EtOAc:hexane.



2C: Benzyloxycarbonyl (O-*tert*-butyltyrosinyl)valylalanine (11)

This was prepared from 10 on a 5.7 mmol scale by lithium hydroxide hydrolysis in a dioxan/water mixture. The product isolated in 96% yield following flash chromatography on silica gel eluting with 60:2:1 $CHCl_3$:MeOH:AcOH.

2D: *tert*-Butyl (3S, 4RS)-3-(benzyloxycarbonyl(O-*tert*-butyltyrosinyl)valylalanylamino)-4-hydroxy-6-oxa-8,8,8-trifluorooctanoate (12a)

This was prepared from 4 and 11 on a 0.25 mmol scale following the method of Example 1E. The product was isolated in 66% yield after flash chromatography on silica gel eluting with 80:20 EtOAc:hexane.

2E: *tert*-Butyl (3S)-3-(benzyloxycarbonyl(O-*tert*-butyltyrosinyl)valylalanylamino)-6-oxa-4-oxo-8,8,8-trifluorooctanoate (13a)

This was prepared from 12a on a 0.17 mmol scale following the method of Example 1G. The product was isolated in 58% yield after flash chromatography on silica gel eluting with 80:20 EtOAc:hexane.

2F: *tert*-Butyl (3S)-3-(acetyl(O-*tert*-butyltyrosinyl)valylalanylamino)-6-oxa-4-oxo-8,8,8-trifluorooctanoate (14a)

This was prepared from 13a on a 0.099 mmol scale by hydrogenolysis over 10% Pd-on-C in methanol and subsequent acetylation with acetic anhydride in a mixture of dichloromethane and DMF. The product was isolated in 70% yield after flash chromatography on silica gel eluting with 100:2 EtOAc:AcOH.

2G: (3S)-3-(Acetyltyrosinylvalylalanylamino)-6-oxa-4-oxo-8,8,8-trifluorooctanoic acid (15a)

This was prepared from 14a on a 0.07 mmol scale following the method of Example 1H. The product was purified by MPLC on a Vydac C_{18} column using a gradient of 10:90:0.1 to 60:40:0.1 MeCN:H_2O:TFA to give the title compound as an amorphous solid (6 mg, 14%).

HPLC: Gradient 10 to 70% B into A in 25 min at 0.8 mL/min.
Peak detected at 11.6'.

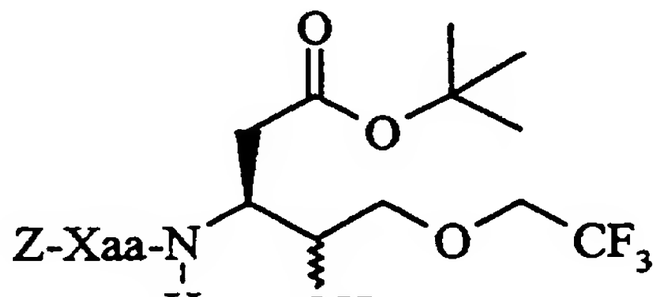
A.A.A.: Found: Ala 1.00; Tyr 0.99; Val 1.01.
P.C. = 74%.

M.S.: $[M+H]^+ = 605.3$.

Examples 3 - 15

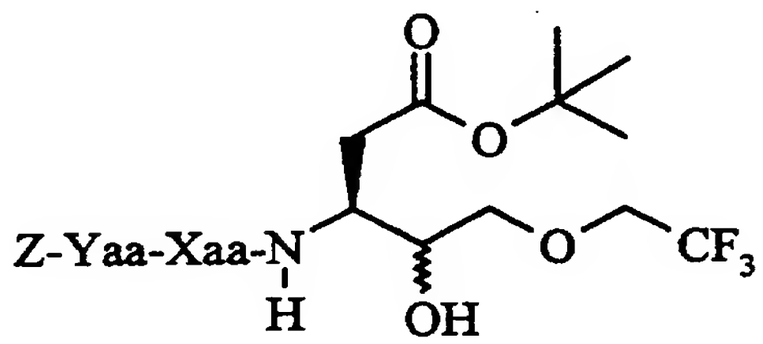
Following the route described in Example 1 the following compounds were prepared.

Table A: Analogues of 5a prepared following the method of Example 1E.



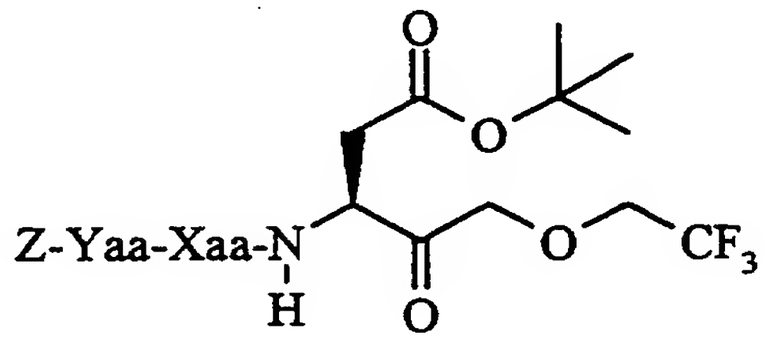
Product	Xaa	Scale (mmol)	Yield (%)	Column
5b	Ile	0.7	43	60:40 E:P
5c	Hph	0.7	34	55:45 E:P
5d	Val	0.75	45	55:45 E:P
5e	Aha	0.75	49	55:45 E:P
5f	Pro	0.70	50	65:35 E:P

Table B: Analogues of 6aa prepared following the method of Example 1F.



Starting Material	Product	Yaa	Xaa	Scale (mmol)	Yield (%)	Column
5a	6ab	Phe	Ala	0.3	78	80:20 E:P
	6ac	Hph		0.36	85	65:35 E:P
	6ad	Aha		0.40	79	75:25 E:P
	6ae	Pro		0.40	85	95:5 E:P
	6af	Phg		0.45	69	65:35 E:P
	6ag	Leu		0.45	73	70:30 E:P
	6ah	Ile		0.45	85	70:30 E:P
	6ai	Chg		0.45	77	70:30 E:P
5b	6ba	Val	Ile	0.30	74	70:30 E:P
5c	6ca		Hph	0.24	73	70:30 E:P
5d	6da		Val	0.34	89	65:35 E:P
5e	6ea		Aha	0.37	91	65:35 E:P
5f	6fa		Pro	0.70	50	65:35 E:P

Table C: Analogues of 7aa prepared following the method of Example 1G.



Product	Yaa	Xaa	Scale (mmol)	Yield (%)	Column
7ab	Phe	Ala	0.23	72	65:35 E:P
7ac	Hph		0.36	85	65:35 E:P
7ad	Aha		0.31	80	65:35 E:P
7ae	Pro		0.34	63	80:20 E:P
7af	Phg		0.31	67	60:40 E:P
7ag	Leu		0.33	68	60:40 E:P
7ah	Ile		0.38	72	60:40 E:P
7ai	Chg		0.35	73	60:40 E:P
7ba	Val	Ile	0.22	79	55:45 E:P
7ca		Hph	0.18	57	50:50 E:P
7da		Val	0.30	50	50:50 E:P
7ea		Aha	0.34	50	45:55 E:P
7fa		Pro	0.32	85	60:40 E:P

Table D: Analogues of 8aa prepared following the method of Example 1H.

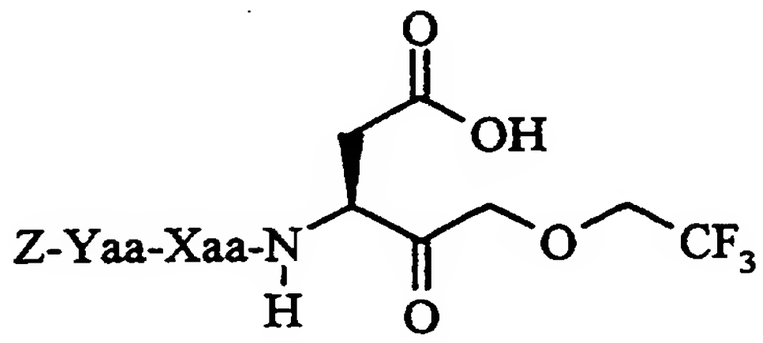


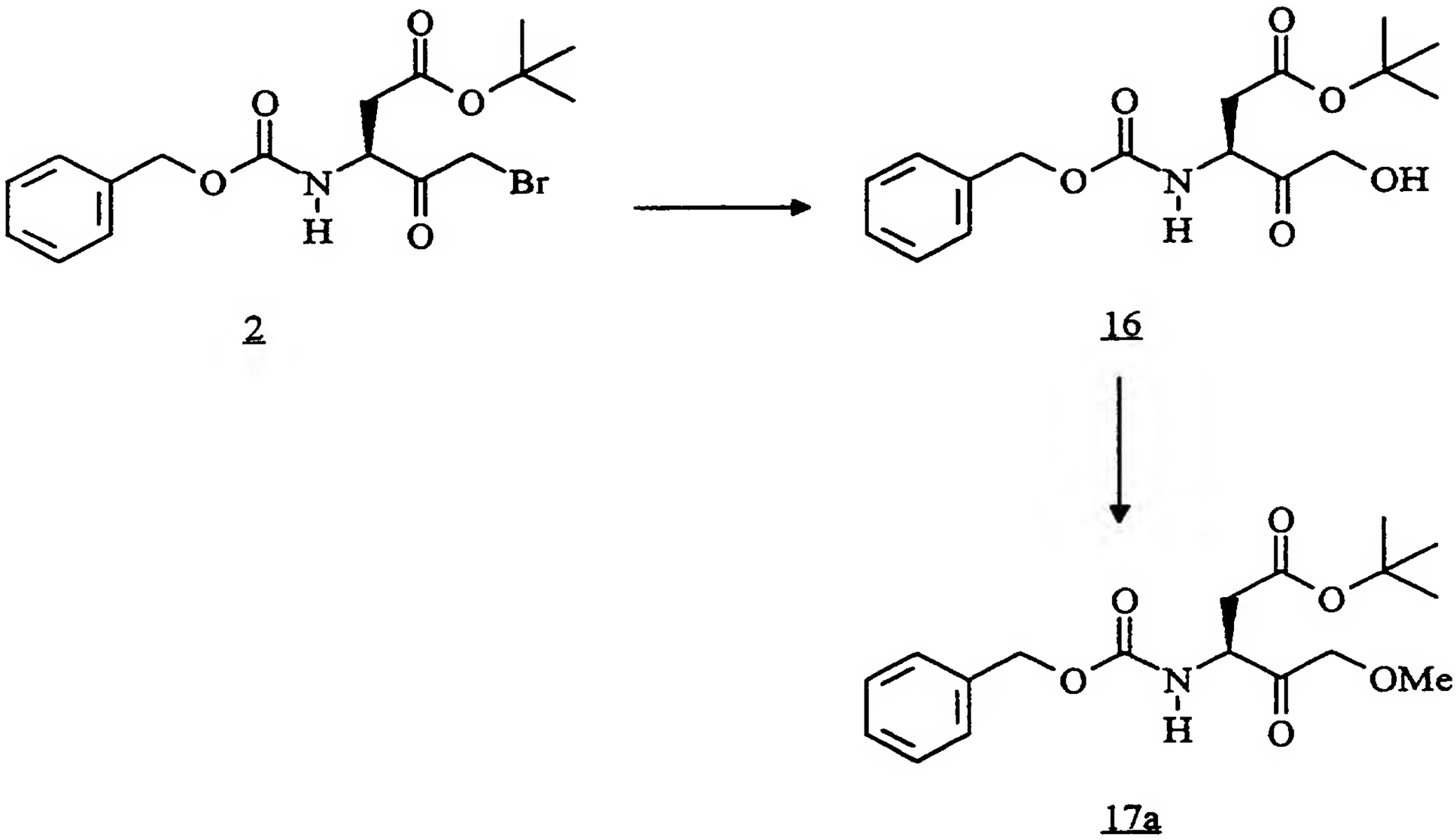
Table D1

Example	Product	Yaa	Xaa	Scale (mmol)	Yield (%)
3	8ab	Phe	Ala	0.16	16
4	8ac	Hph		0.31	53
5	8ad	Aha		0.25	52
6	8ae	Pro		0.21	82
7	8af	Phg		0.21	69
8	8ag	Leu		0.22	88
9	8ah	Ile		0.27	68
10	8ai	Chg		0.26	62
11	8ba	Val	Ile	0.17	47
12	8ca		Hph	0.10	61
13	8da		Val	0.15	52
14	8ea		Aha	0.17	50
15	8fa		Pro	0.27	74

Table D2

Example	Column	MPLC	HPLC	AAA: Found	PC (%)	M.S.
3	60:2:1 C:M:A	30% to 70%	A 15.6'	Ala 0.99 Phe 1.01	87	582.1
4	60:2:1 C:M:A	30% to 70%	A 16.5'	Ala 1.00 Hph 1.00	86	596.2
5	60:2:1 C:M:A	25% to 75%	A 15.0'	Ala 0.98 Aha 1.02	88	548.3
6	30:2:1 C:M:A	20% to 70%	A 12.0'	Ala 1.00 Pro 1.00	83	532.2
7	50:2:1 C:M:A	25% to 75%	A 15.0'	Ala 0.99 Phg 1.01	84	568.2
8	50:2:1 C:M:A	25% to 70%	A 15.3'	Ala 0.97 Leu 1.03	77	548.2
9	50:2:1 C:M:A	25% to 70%	A 15.0'	Ala 1.01 Ile 0.99	82	548.2
10	50:2:1 C:M:A	30% to 70%	A 16.5'	Ala 0.99 Chg 1.01	82	574.2
11	70:2:1 C:M:A	30% to 70%	A 16.4'	Ile 0.94 Val 1.06	81	576.4
12	70:2:1 C:M:A	30% to 75%	B 10.5'	Hph 0.99 Val 1.01	77	624.4 -
13	70:2:1 C:M:A	30% to 70%	A 15.6'		83	562.3
14	70:2:1 C:M:A	30% to 70%	A 17.0'	Aha 1.00 Val 1.00	84	576.2
15	50:2:1 C:M:A	25% to 70%	A 14.6'	Pro 1.01 Val 0.99	83	560.3

Examples 16 - 18



2 16 17a

16A: *tert*-Butyl (3S)-3-(benzyloxycarbonylamino)-5-hydroxy-4-oxopentanoate (16)

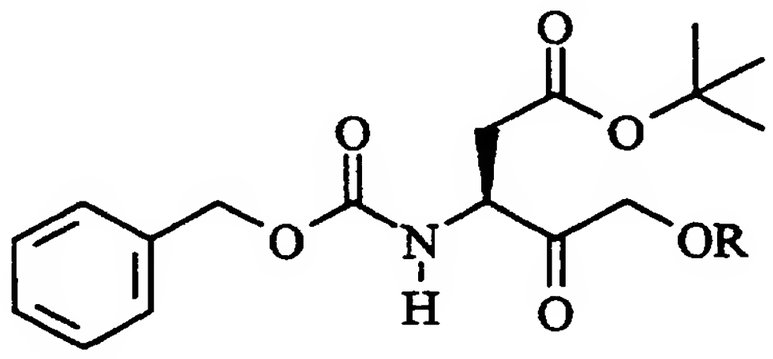
To a stirred solution of the bromomethyl ketone 2 (4.3 g, 10.8 mmol) in DMF (30 mL) was added benzoylformic acid (1.94 g, 12.9 mmol) and cesium fluoride (2.45 g, 16.1 mmol). The mixture was stirred at room temperature for 16 hr then diluted with EtOAc (100 mL) and washed with 1M hydrochloric acid (3 x 75 mL) and brine, filtered and concentrated in vacuo. The residue was taken up in THF (40 mL), aqueous KOH (10.8 mL, 1M, 10.8 mmol) was added, and the mixture was stirred at room temperature for 16 hr. The solvent was evaporated in vacuo and the residue was partitioned between EtOAc (70 mL) and water (50 mL). The aqueous layer was extracted with EtOAc (2 x 70 mL) and the combined organic phases were washed with brine, filtered and concentrated in vacuo. The residue was purified by flash chromatography on silica gel eluting with 45:55 EtOAc:hexane to give the title compound as a colourless oil (3.14 g, 86%).

16B: *tert*-Butyl (3S)-3-(benzyloxycarbonylamino)-4-oxo-5-methoxy-pentanoate (17a)

To a stirred solution of the alcohol 16 (1g, 2.96 mmol) was added iodomethane (1.38 mL, 22.2 mmol) and silver (I) oxide (1.37 g, 5.92 mmol). The mixture was heated at reflux in the dark for 18 hr then allowed to cool and filtered. The filtrate was concentrated in vacuo and the residue was purified by flash chromatography on silica gel eluting with 30:70 EtOAc:hexane to give the title compound as a colourless oil (670 mg, 64%).

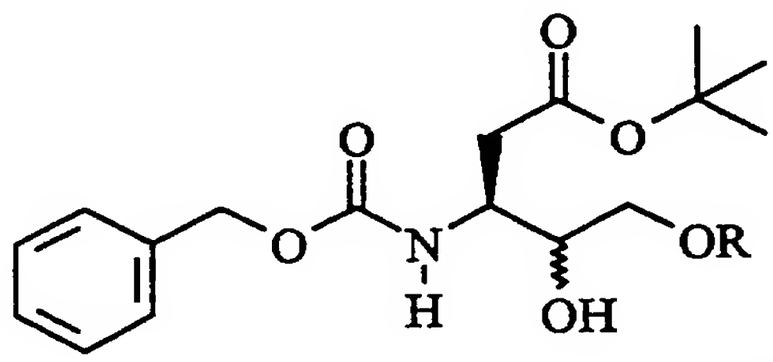
^{1}H NMR ($CDCl_3$): δ 4.69 - 4.28 (2H, isolated AB); 3.45 (3H, s).

Table E: Analogues of 17a prepared following the method of Example 16B.



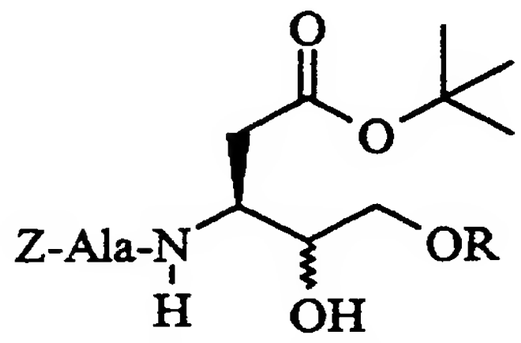
Product	R	Scale (mmol)	Yield (%)	Column	NMR
17b	Et	2.95	39	30:70 E:H	4.25 (2H, ABq), 3.55 (2H, q)
17c	Bu	2.95	20	15:85 E:H	4.22 (2H, ABq), 3.47 (2H, t)
17d	Pr	1.50	25	20:80 E:H	4.28 (2H, ABq), 3.42 (2H, E)

Table F: Analogues of 4 prepared following the method of Example 1D.



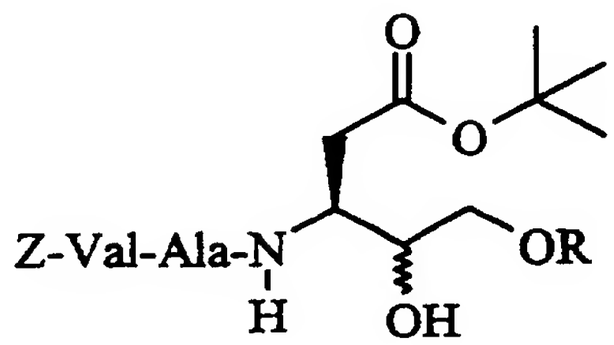
Product	R	Scale (mmol)	Yield (%)	Column	NMR
18a	Me	1.91	84	45:55 E:H	3.45 (2H, m), 3.36 and 3.35 (3H, 2 x s)
18b	Et	1.16	94	45:55 E:H	4.06 (2H, m), 3.50 (2H, q)
18c	Bu	0.58	70	35:65 E:H	4.06 (2H, m), 3.42 (2H, t)
18d	Pr	0.37	67	30:70 E:H	3.54 - 3.32 (4H, m)

Table G: Analogues of 5a prepared following the method of Example 1E.



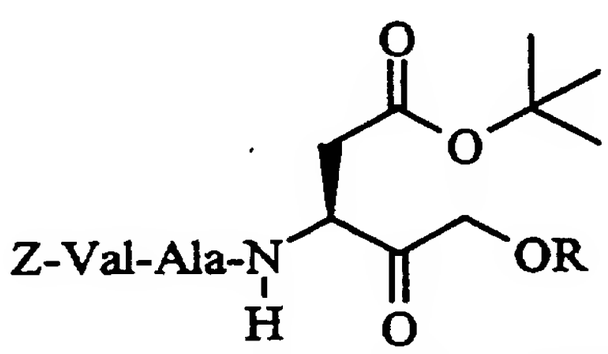
Product	R	Scale (mmol)	Yield (%)	Column	NMR
19a	Me	1.28	61	90:10 E:H	3.46 - 3.28 (2H, m), 3.35 and 3.33 (3H, 2 x s)
19b	Et	1.09	68	90:10 E:H	4.22 (2H, m), 3.46 (2H, q)
19c	Bu	0.40	75	80:20 E:H	4.13 (2H, m), 3.43 (2H, t)

Table H: Analogues of 6aa prepared following the method of Example 1F.



Product	R	Scale (mmol)	Yield (%)	Column	
20a	Me	1.28	61	90:10	E:H
20b	Et	0.74	92	100:1.2	C:M
20c	Bu	0.30	84	100:0.75	C:M

Table I: Analogues of 7aa prepared following the method of Example 1G.



Product	R	Scale (mmol)	Yield (%)	Column		NMR
21a	Me	0.78	61	75:25	E:H	4.23 (2H, ABq), 3.40 (3H, s)
21b	Et	0.68	63	70:30	E:H	4.25 (2H, ABq), 3.54 (2H, q)
21c	Bu	0.25	85	60:40	E:H	4.21 (2H, ABq), 3.47 (2H, t)

Table J: Analogues of 8aa prepared following the method of Example 1H.

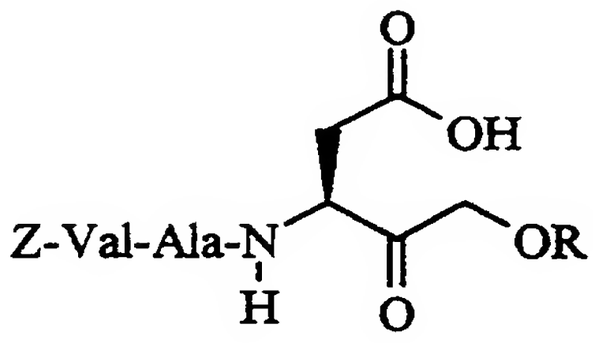


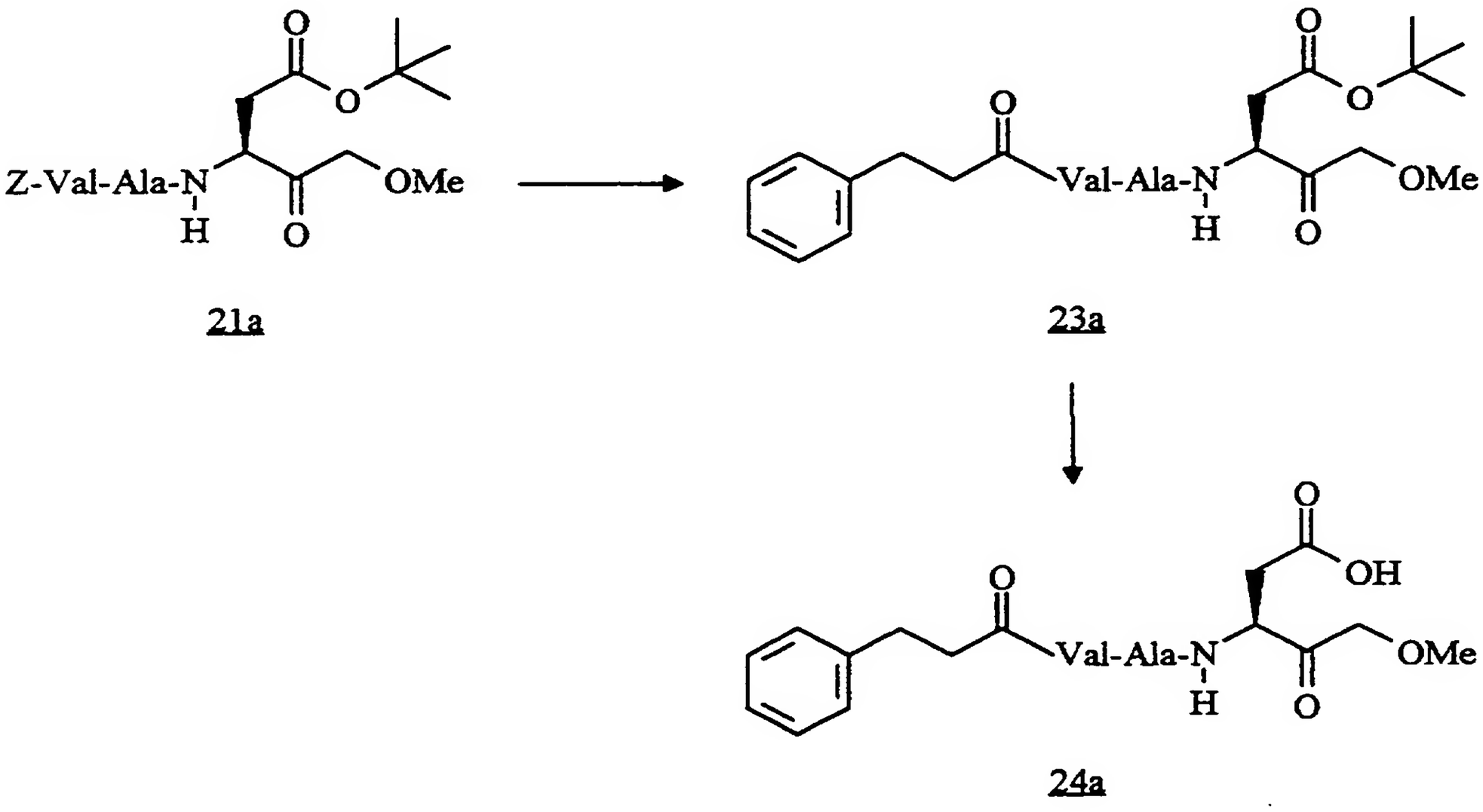
Table J1

Example	Product	R	Scale (mmol)	Yield (%)
16	22a	Me	0.14	37
17	22b	Et	0.13	40
18	22c	Bu	0.21	17

Table J2

Example	MPLC	HPLC	AAA: Found	PC (%)	M.S.
16	15% to 60%	D 4.0'	Ala 1.15 Val 0.85	84	464.2
17	15% to 60%	D 5.0'	Ala 0.88 Val 1.12	81	478.2
18	20% to 80%	C 9.6'	Ala 1.00 Val 1.00	83	508.2

Example 19: (3S)-5-Methoxy-4-oxo-3-(3-phenylpropionylvalylalanylamino)pentanoic acid



21a

23a

24a

19A: *tert*-Butyl (3S)-5-methoxy-4-oxo-3-(3-phenylpropionylvalylalanylamino)pentanoate (23a)

This was prepared from 21a on a 0.24 mmol scale by sequential hydrogenolysis and hydroxybenzotriazole-mediated coupling to phenylpropionic acid following the method of Example 1E. The product was isolated in 56% yield after flash chromatography on silica gel eluting with ethyl acetate.

19B: (3S)-5-Methoxy-4-oxo-3-(3-phenylpropionylvalylalanylamino)pentanoic acid (24a)

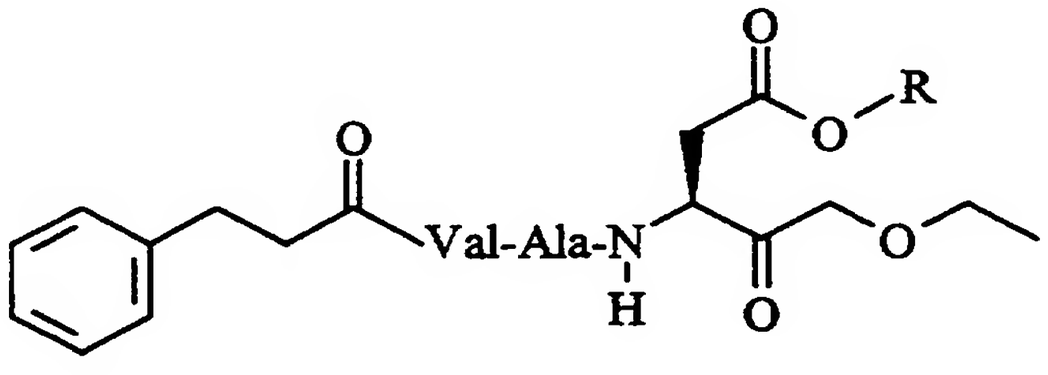
This was prepared from 23a on a 0.14 mmol scale following the method of Example 1H. The product was purified by MPLC on a Vydac C_{18} column eluting with a gradient of 15:85:0.1 to 60:40:0.1 MeCN:H_2O:TFA and isolated as an amorphous solid (24 mg, 37%).

HPLC: Gradient 30 to 90% B into A in 25 min at 0.8 mL/min.
Peak detected at 4.0'.

A.A.A.: Found: Ala 0.85; Val 1.15.
P.C. = 84%.

M.S. $[M+H]^+ = 464.2$.

Example 20: (3S)-5-Ethoxy-4-oxo-3-(3-phenylpropionylvalylalanylamino)pentanoic acid



23b R = t-Bu

24b R = H

Following the methods of Example 19, 21b was converted on a 0.21 mmol scale into 23b in 62% yield (column eluant EtOAc) which was then converted on a 0.13 mmol scale into 24b which was isolated in 40% yield after MPLC on a Vydac C_{18} column eluting with a gradient of 15:85:0.1 to 60:40:0.1 MeCN:H_2O:TFA.

HPLC: Gradient: 30 to 90% B into A in 25 min at 0.8 mL/min.
Peak detected at 5.0'.

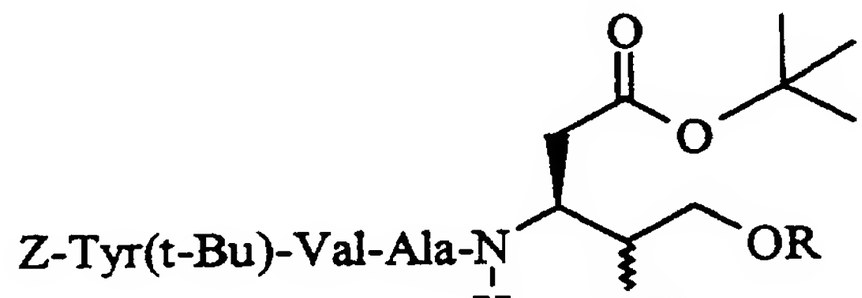
A.A.A.: Found: Ala 0.88; Val 1.12.
P.C. = 81%.

M.S.: $[M+H]^+ = 478.2$.

Examples 21 - 22

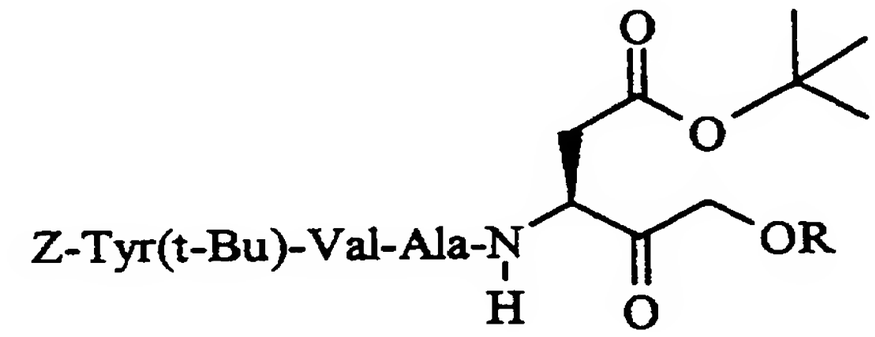
Following the route described in Example 2 the following compounds were prepared.

Table K: Analogues of 12a prepared following the method of Example 2D.



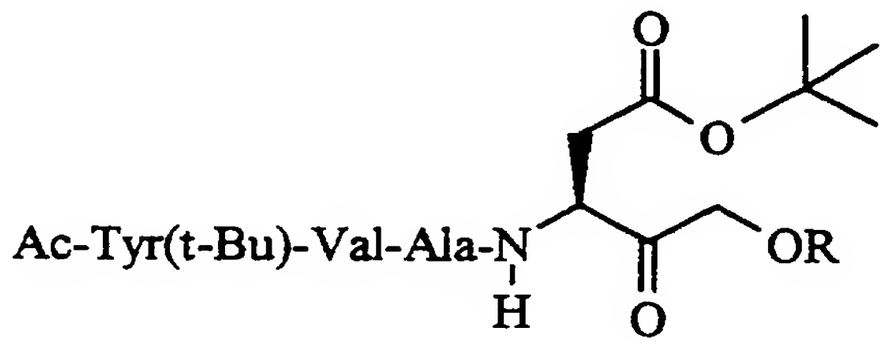
Starting Material	Product	R	Scale (mmol)	Yield (%)	Column
18b	12b	Et	0.65	67	100:2 E:A
18d	12c	Pr	0.25	65	85:15 E:H

Table L: Analogues of 13a prepared following the method of Example 2E.



Product	R	Scale (mmol)	Yield (%)	Column
13b	Et	0.44	55	75:25 E:H
13c	Pr	0.16	88	80:20 E:H

Table M: Analogues of 14a prepared following the method of Example 2F.



Product	R	Scale (mmol)	Yield (%)	Column
14b	Et	0.24	60	100:2 E:A
14c	Pr	0.14	81	100:1 E:A

Table N: Analogues of 15a prepared following the method of Example 2G.

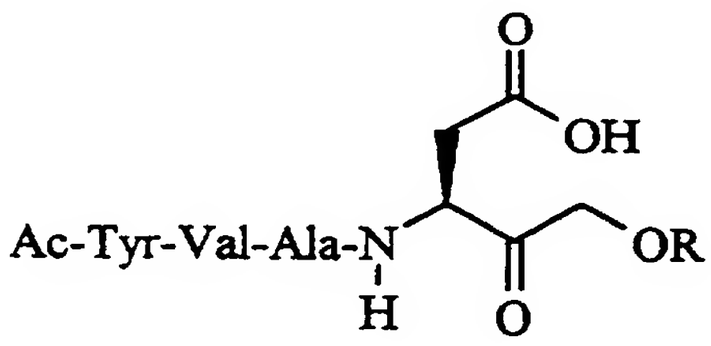


Table N1

Example	Product	R	Scale (mmol)	Yield (%)
21	15b	Et	0.15	15
22	15c	Pr	0.11	19

Table N1

Example	MPLC	HPLC	AAA: Found	PC (%)	M.S.
21	15% to 70%	D 8.4'	Ala 1.00, Tyr 1.01, Val 0.99	84	551.8
22	15% to 70%	D 10.1'	Ala 1.00, Tyr 0.95, Val 1.05	76	565.2

The Compounds of the present Invention reversibly inhibit the proteolytic action of interleukin-1β converting enzyme (ICE) with high potency. This activity can be demonstrated and quantified as follows.

Determination of K_i

Compounds were assayed using a COBAS FARA II centrifugal analyser (Roche Diagnostics). All substrate and inhibitor solutions were made by diluting a 10mM DMF stock into standard assay buffer 10mM HEPES NaOH pH 7.5, 10% sucrose, 0.1% CHAPS, 1mM EDTA. Ac-Tyr-Val-Ala-Asp-AFC substrate concentrations used in the assay were 10, 20 and 30 μM and inhibitor concentrations used in the assay were varied from $0.5xK_i$ to $20xK_i$. Enzyme solution was prepared by reactivating 50μL ICE-glutathione conjugate [N.A. Thornberry *et al. Nature* **356**, 768-774 (1992)] (5,000 unit/mL) in 2.3 mL assay buffer containing 50 mM DTT, where 1 unit of activity≡1 pmole AFC min^{-1}.

30 μL Inhibitor (x10 conc.), 30 μL substrate (x10 conc.) and 180μL assay buffer were mixed together by centrifugal vortexing. Then 60μL freshly prepared enzyme solution (6 unit) was added and this was mixed with the substrate and inhibitor by centrifugal vortexing. The assay was then incubated at 37°C and fluorimetric readings (excitation 395nm, emission 515nm) were taken after 2 min and every 2 min thereafter for 20 min.

The rate of AFC production was determined for several inhibitor concentrations at each of three substrate concentrations, and the steady state K_i value was determined by the method of Dixon [Dixon H.B.F. *Biochem. J.* **55**, 170-171 (1953)] using the ENZFITTER program (Biosoft, Camb. UK).

Typical values for the dissociation constant K_i are as follows:

Compound of Example	K_i (nM)
1	64
2	38
3	180
4	450
5	370
6	19000
7	1500
8	530
9	470
10	770
11	180
12	100
13	200
14	92
15	57
16	790
17	330
18	41
19	1500
20	630
21	115
22	55

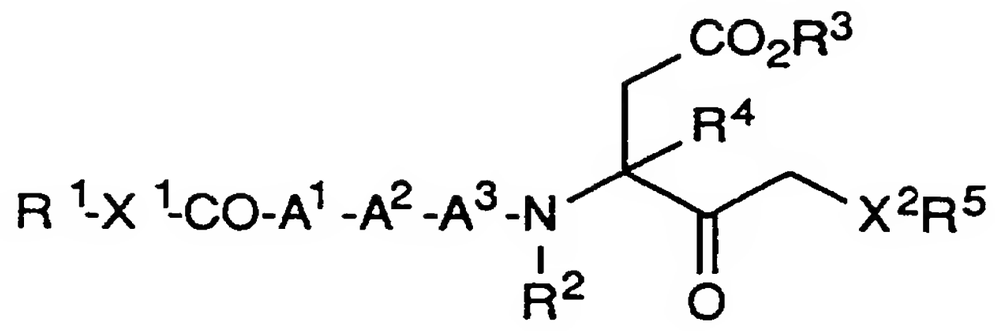
As described above, this inhibition of ICE *in vitro* can be expected to translate into an anti-inflammatory activity in vivo. Thus a further aspect of the present Invention is the treatment of a disease in which interleukin-1β is a causative factor. Examples of such diseases include,

but are not limited to, rheumatoid arthritis, encephalitis, inflammatory bowel disease, pancreatitis, psoriasis, hypotensive shock and reperfusion injury following myocardial infarction.

The compounds of the present Invention can be administered in ways which are well known in the Art. For example they may be administered orally as tablets or capsules, by intravenous or intramuscular injection, or by topical, transdermal or rectal application. Depending on the route of administration the compounds will be formulated in an appropriate manner. The dosage required will be determined by the physician taking into account all the relevant factors and will typically be between 1mg and 1000mg either once per day or in repeated doses.

Claims

1. A compound of formula I



I

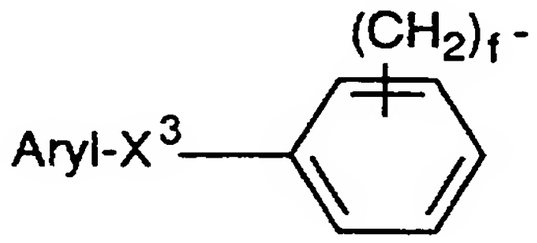
or a pharmaceutically acceptable salt thereof wherein:

R^1 is

(a) substituted alkyl C_1 - C_6, wherein the substituents are selected from hydrogen, halogen, hydroxy, C_1 - C_6 alkoxy, C_1 - C_6 alkylcarbonyl and phenyl;

(b) aryl or aryl C_1 - C_6 alkyl wherein the aryl group is selected from phenyl, napthyl, pyridyl, furyl, thienyl, thiazolyl, isothiazolyl, imidazolyl, benzimidazolyl, pyrazinyl, pyrimidyl, quinolyl, isoquinolyl, benzofuryl, benzothienyl, pyrazolyl, indolyl, purinyl, isoxazolyl, oxazolyl, quinoxalinyl, triazolyl and triazinyl, and mono and di-substituted aryl as defined above wherein the substituents are independently C_1 - C_6 alkyl, halo, hydroxy, NR^6R^7, C_1 - $_6$ alkoxy, C_{1-6} alkylthio, C_1 - $_6$ alkylcarbonyl, carboxy or phenyl;

(c)



II;

wherein aryl is defined as in (b) above, and may be substituted as defined in (b) above.

R^2 is hydrogen, alkyl C_{1-4}, benzyl;

R^3 is hydrogen, alkyl C_{1-4} or phenyl;

R^4 is hydrogen, fluorine, C_{1-4} alkyl, $-(CH_2)_a-CO_2H$;

R^5 is

(a) substituted alkyl C_{1-10}, wherein the substituents are selected from hydrogen, halogen, hydroxy, C_{1-6} alkoxy;

(b) aryl alkyl C_{1-6} wherein the alkyl groups may be substituted by hydrogen, halogen or hydroxy and the aryl group is selected from phenyl, pyridyl or napthyl, and is optionally mono or di-substituted with the substituents being selected independently from C_{1-6} alkyl, halo, hydroxy, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkylcarbonyl, carboxy or phenyl;

(c) aryl or substituted aryl as defined in (b) above, subject to R^4 not being hydrogen and/or at least two of A^1, A^2 and A^3 being absent, and/or X^2 being -OCONH-, $-NHCO_2-$ or -NHCONH-;

R^6 and R^7 are independently hydrogen or C_{1-4} alkyl;

R^8, R^{10} and R^{12} are each independently selected from hydrogen or alkyl C_{1-6};

R^9, R^{11} and R^{13} are each independently selected from

(a) hydrogen

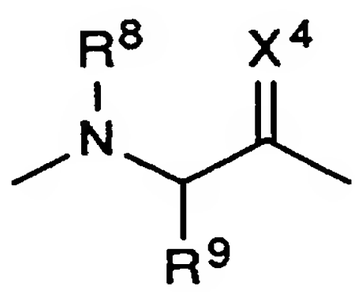
(b) substituted saturated or unsaturated alkyl C_{1-6}, wherein the substituent is selected from hydrogen, hydroxy, halo, -SH, $-S-C_{1-4}$ alkyl, C_{1-6} alkylcarbonyl, carboxy, $-CONH_2$, amino, C_{1-4} alkylamino, guanidino, $-O-C_{1-4}$ alkyl, phenylcarbonylamino;

(c) aryl or aryl C_{1-6} alkyl, wherein aryl is phenyl, pyridyl, indolyl or imidazolyl and wherein the aryl is optionally mono and di-substituted, the substituents being each independently C_{1-4} alkyl, halo, hydroxy, CO_2H, Me_2N-, NH_2, C_{1-4} alkylamino, C_{1-4} alkoxy, C_{1-4} alkylthio, C_{1-4} alkyl carbonyl, NO_2, -SH or -CN;

A^1 is selected from

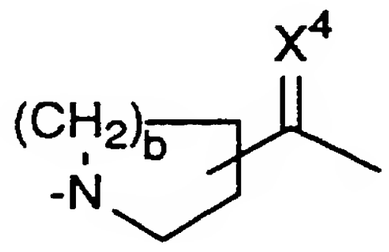
(a) a single bond;

(b) an amino acid residue or analogue of formula III;



III

(c) an imino acid residue or analogue of formula IV;

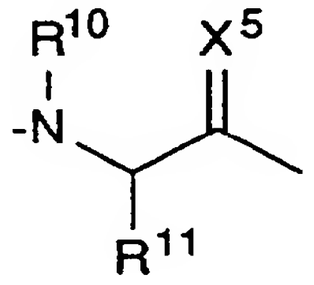


IV

A^2 is selected from

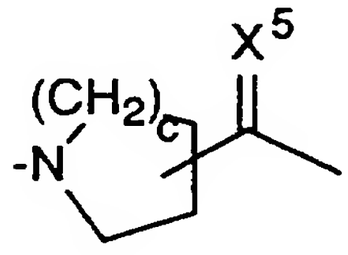
(a) a single bond;

(b) an amino acid residue or analogue of formula V;



V

(c) an imino acid residue or analogue of formula VI;

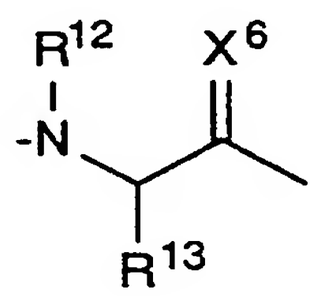


VI

A^3 is selected from

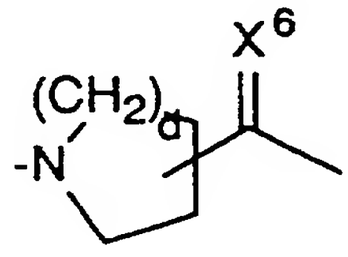
(a) a single bond;

(b) an amino acid residue or analogue of formula VII;



VII

(c) an imino acid residue or analogue of formula VIII



VIII

X^1 is absent, -O- or -NH-;

X^2 is -O-, -S-, -OCONH-, -$NHCO_2$- or -NHCONH-;

X^3 is absent, -NH-, -$(CH_2)_e$-, -$(CH_2)_eO$-, -$O(CH_2)_e$-, -CH=CH-, -$CO(CH_2)_e$-, -$(CH_2)_eCO$-, -$(CH_2)_eNHCO$-, -$NHCO(CH_2)_e$-, -$(CH_2)_eCONH$-, -$CONH(CH_2)_e$-, -$(CH_2)_eNHSO_2$-, -$NHSO_2(CH_2)_e$-, -$SO_2NH(CH_2)_e$-, -$(CH_2)_eSO_2NH$-, -$(CH_2)_eNH$-, -$NH(CH_2)_e$-;

X^4, X^5 and X^6 are each independently O or H_2;

a is 0 - 3

b is 0 - 4

c is 0 - 4

d is 0 - 4

e is 0 - 3

f is 0 - 2

2. A compound according to claim 1 wherein:

A^1 is a residue of tyrosine, phenylalanine, homophenylalanine, phenylglycine, tryptophan or histidine;

R^1 is unsubstituted C_{1-6} alkyl;

X^1 is absent.

3. A compound according to claim 2 wherein:

R^4 is hydrogen;

R^5 is substituted alkyl C_{1-10}, wherein the substituents are selected from hydrogen, halogen, hydroxy, C_{1-6} alkoxy or phenyl;

X^2 is O or S.

4. A compound of claim 1 wherein:

R^1 is aryl or aryl C_{1-6} (saturated or unsaturated) alkyl wherein the aryl group is selected from phenyl, napthyl, pyridyl, furyl, thienyl, pyrazinyl, pyrimidinyl, pyrazolyl and indolyl, and mono and disubstituted aryl as defined above wherein the substituents are independently C_{1-6} alkyl, halo, hydroxy, NR^6R^7, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkyl carbonyl, carboxy or phenyl;

A^1 is absent;

5. A compound of claim 4 wherein:

R^4 is hydrogen;

R^5 is substituted alkyl C_{1-10}, wherein the substituents are selected from hydrogen, halogen, hydroxy, C_{1-6} alkoxy, or phenyl;

X^2 is O or S.

6. A compound of claim 1 where both A^1 and A^2 are absent.

7. A compound of claim 1 where R^4 is methyl.

8. At least one compound selected from the following compounds according to claim 1 and pharmaceutically acceptable salts thereof:

(3S)-3-(Acetyl-tyrosinyl-valyl-alanyl)amino-4-oxo-5-(2',2',2'-trifluoroethoxy) pentanoic acid;

(3S)-3-(Acetyl-tyrosinyl-valyl-alanyl)amino-4-oxo-5-^{n}propyloxy pentanoic acid;

(3S)-3-(Acetyl-tyrosinyl-valyl-alanyl)amino-5-ethoxy-4-oxo pentanoic acid;

(3S)-3-(Benzyloxycarbonyl-valyl-alanyl)amino-4-oxo-5-(2',2',2'-trifluoroethoxy) pentanoic acid;

(3S)-3-(Benzyloxycarbonyl-valyl-alanyl)amino-5-methoxy-4-oxo pentanoic acid;

(3S)-3-(Benzyloxycarbonyl-valyl-alanyl)amino-5-^{n}butyloxy-4-oxo pentanoic acid;

(3S)-3-(Benzyloxycarbonyl-valyl-alanyl)amino-5-ethoxy-4-oxo pentanoic acid;

(3S)-3-(Benzyloxycarbonyl-phenylalanyl-alanyl)amino-4-oxo-5-(2',2',2'-trifluoroethoxy) pentanoic acid;

(3S)-3-(Benzyloxycarbonyl-homophenylalanyl-alanyl)amino-4-oxo-5-(2',2',2'-trifluoroethoxy) pentanoic acid;

(3S)-3-(Benzyloxycarbonyl-norleucinyl-alanyl)amino-4-oxo-5-(2',2',2'-trifluoroethoxy) pentanoic acid;

(3S)-3-(Benzyloxycarbonyl-prolyl-alanyl)amino-4-oxo-5-(2',2',2'-trifluoroethoxy) pentanoic acid;

(3S)-3-(Benzyloxycarbonyl-phenylglycinyl-alanyl)amino-4-oxo-5-(2',2',2'-trifluoroethoxy) pentanoic acid;

(3S)-3-(Benzyloxycarbonyl-leucinyl-alanyl)amino-4-oxo-5-(2',2',2'-trifluoroethoxy) pentanoic acid;

(3S)-3-(Benzyloxycarbonyl-isoleucinyl-alanyl)amino-4-oxo-5-(2',2',2'-trifluoroethoxy) pentanoic acid;

(3S)-3-(Benzyloxycarbonyl-cyclohexylglycinyl-alanyl)amino-4-oxo-5-(2',2',2'-trifluoroethoxy) pentanoic acid;

(3S)-3-(Benzyloxycarbonyl-valyl-isoleucyl)amino-4-oxo-5-(2',2',2'-trifluoroethoxy) pentanoic acid;

(3S)-3-(Benzyloxycarbonyl-valyl-norleucyl)amino-4-oxo-5-(2',2',2'-trifluoroethoxy) pentanoic acid;

(3S)-3-(Benzyloxycarbonyl-valyl-homophenylalanyl)amino-4-oxo-5-(2',2',2'-trifluoroethoxy) pentanoic acid;

(3S)-3-(Benzyloxycarbonyl-valyl-valyl)amino-4-oxo-5-(2',2',2'-trifluoroethoxy) pentanoic acid;

(3S)-3-(Benzyloxycarbonyl-valyl-propyl)amino-4-oxo-5-(2',2',2'-trifluoroethoxy) pentanoic acid;

(3S)-5-Methoxy-4-oxo-3-(3'-phenylpropanoyl-valyl-alanyl)amino pentanoic acid;

(3S)-5-Ethoxy-4-oxo-3-(3'-phenylpropanoyl-valyl-alanyl)amino pentanoic acid;

(3S)-3-(Benzoyl-valyl-alanyl)amino-5-^{n}butyloxy-4-oxo pentanoic acid;

(3S)-3-(Benzoyl-valyl-alanyl)amino-5-benzyloxy-4-oxo pentanoic acid;

(3S)-3-(Benzoyl-valyl-alanyl)amino-4-oxo-5-(3'-hydroxypropyloxy) pentanoic acid.

9. A pharmaceutical composition for treatment of interleukin-1 mediated disorders or diseases in a patient in need of such treatment comprising of a compound according to claim 1 as the active constituent.

Patents Act 1977 46 Examiner's report to the Comptroller under Section 17 (T Search report)	Application number GB 9416078.5
Relevant Technical Fields (i) UK Cl (Ed.M) C3H (HA4) (ii) Int Cl (Ed.5) C07K 5/02	Search Examiner C SHERRINGTON Date of completion of Search 1 NOVEMBER 1994
Databases (see below) (i) UK Patent Office collections of GB, EP, WO and US patent specifications. (ii) ONLINE DATABASES: CAS ONLINE, CHABS	Documents considered relevant following a search in respect of Claims :- 1 to 9

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E: Patent document published on or after, but with priority date earlier than, the filing date of the present application.

&: Member of the same patent family; corresponding document.

Category	Identity of document and relevant passages	Relevant to claim(s)
A	WO 93/16710 A1 (MERCK & CO INC) Whole document	1
A	WO 93/09135 A1 (SANDOZ LTD) Whole document	1
A	EP 0547699 A1 (MERCK & CO INC) Whole document	1
A	Biochemistry 1994, 33(13), 3934-3940 Inactivation of Interlenkin - 1 Beta Converting Enzyme by Peptide (Acyloxy) Methyl Ketones	1
A	J Med. Chem. 1994, 37(5), 563-564 P1 Aopartate-Based Peptide Alpha ((2,6-Dichlorobenzoyl)oxy) Methyl Ketones as...	1

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